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RETROSPECTIVE STUDY ON ANENCEPHALY AND ITS CORRELATION WITH OTHER NEURAL TUBE DEFECTS

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Abstract: *Anencephaly is a neural tube defect where parts of the cerebrum are not developed. Data used in this study contains the prevalence of neural tube defects from 1992 to 2015 and it was extracted from the online data library HealthData.gov. 285 cases with anencephaly, 1540 cases with spina bifida and 473 cases with encephalocele were involved in the study. A 22% decrease of anencephaly was obtained after folate fortification. There is a strong correlation between the birth year and the number of cases from the respective year in anencephalic fetus (R = - 0,59). Anencephaly case count correlates moderately to spina bifida and encephalocele(R = 0,41, respectively R = 0,43). Mandatory fortification with folic acid led to a decrease in anencephaly and spina bifida prevalence, but encephalocele's prevalence remained constant since the mandatory fortification.*

INTRODUCTION

Congenital anomalies are morphological anomalies that occur in the intrauterine life. These can be accompanied or not by function and are also known as birth defects. Even though most congenital anomalies cannot be linked to a specific cause, some known causes of congenital defects include genetic mutations, multifactorial disorders, chromosomal disorders, teratogens agents.(1) Neural tube defects (NTD) are congenital anomalies caused by the insufficient closure of the neural tube during gastrulation, including anencephaly, spina bifida and encephalocele.

Folic acid fortification was first introduced in pregnancies with previous history of NTD in 1991. In 1992, The U.S. Public Health Service recommended for all females who can become pregnant 400 micrograms of folic acid per day in order to prevent NTD. In 1998, The Institute of Medicine's Food and Nutrition Board of the National Academy of Sciences recommended, aside from the 400 micrograms, to consume food with folic acid to reduce the chance of having a child with a neural tube defect.(2)

Anencephaly is a neural tube defect that happens when the anterior neuropore does not close completely in the first month of gestation. As a result, the brain and the skull will fail to develop. Often, large portions of the skull, scalp and the brain are absent. The cause of the defect is not known; however, teratogens and socio-economic factors have been associated with anencephaly.(3)

AIM

This study aims to determine trends in anencephaly and to correlate the results with other neural tube defects.

MATERIALS AND METHODS

The dataset was extracted from the online data library HealthData.gov (4) and it contains the prevalence of birth defects in the state of New York from 1992 to 2015. The patients were grouped by their birth year, conditions, sex, residence, the number of patients diagnosed by a certain anomaly, number of live births in that specific year and the prevalence.

Data collected all neural tube defects in children born in the state of New York between 1992 and 2015.

Microsoft Excel was used for data and charts input, and GraphPad was used for descriptive analysis and correlations.

RESULTS

Prevalence

Out of 6.091.548 pregnancies in the state of New York in 1992 -2015 only 285 were presented with anencephaly. The overall prevalence of anencephaly in the state of New York is 0,46 new-borns per 10.000 live births.

Data Analysis

A total of 285 patients presented with anencephaly in 1992–2015, out of which 157 were females and 128 were males.

A confidence level of 95% was used and P values smaller than 0,05 are considered significant. For p values greater than 0,05 the null hypothesis is accepted and for p values smaller than 0,05 the alternate hypothesis is accepted.

After analysing the correlation between the birth defect count with the respective year using Pearson's test, we get the following results:

- R (correlation coefficient) = - 0,5954
- R squared (coefficient of determination) = 0,3545
- p value = 0,0021 which is less than 0,05 so the alternative hypothesis is accepted.

There is a negative, strong correlation between the birth year and the number of cases of anencephaly. Meaning that

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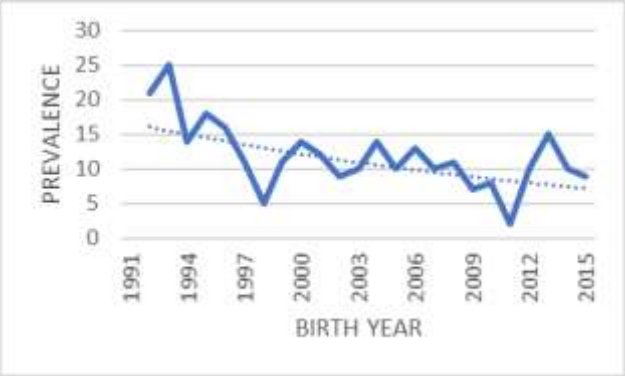
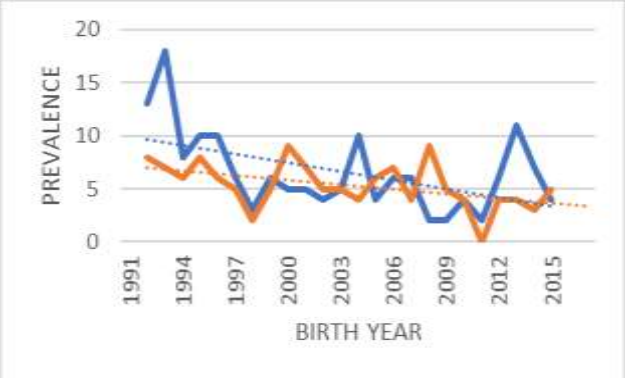
there is a decrease of total cases of anencephaly from 1992 to 2015 with a maximum average of 18,8 in 1992-1997 and an average of 7 (minimum average) in 2010-2015. A 22% decrease in the number of cases of anencephaly was calculated.

Figure no. 1. Anencephaly prevalence evolution during the studied period



Despite Grubbs's test that calculated the number of female cases in 1993 as an outlier it will still be used in the descriptive statistics because it is an intrinsic component of the studied population. For the Wilcoxon test, the two-tailed p value is 0,146, considered not significant. As a result, there is no statistically significant difference between the number of anencephalic males and females, despite the overall difference of 29 cases between the genders.

Figure no. 2. The relationship between the number of males and females born with anencephaly between 1992 and 2015. The blue lines represent the female patient count, the orange lines the male patient count. The interrupted lines represent trendlines for respective populations



During 1992 - 1998 the decline in the number of patients was the most pronounced. This downwards trend can be proven by comparing the average number of cases of both groups studied (female and male) before and, respectively, after 1998 (9.71; 5.23 for females, 6; 5.05 for males). For both groups the averages are greater before 1998. The decrease in the number of female patients is more pronounced than the decrease of number of male patients. As a result, after 2013, the male patient count overpass the female patient count.

Anencephaly correlation with other NTD

Spina bifida is a neural tube defect where the vertebral arch is not closed completely. It manifests in three forms: spina bifida occulta (no protrusion), meningocele (protrusion of the meninges) and myelomeningocele (protrusion of the spinal cord).(5) Encephalocele, another NTD, occurs when the neural tube fails to close during the first month of pregnancy. It manifests as a protrusion of the brain and the meninges.(6)

A total of 1540 patients presented with spina bifida and 473 encephalocele between 1992 and 2015.

After applying Pearson's test to encephalocele's case count and the birth year, a correlation coefficient (R) of -0.14 was obtained, which shows a very weak, negative association. Furthermore, Spearman's test applied to spina bifida case count and the birth year showed a correlation coefficient (R) of -0,52, which suggests a moderate, negative association.

By studying the correlation of anencephaly with spina bifida and encephalocele we get a correlation coefficient (R) of 0,41 and, respectively, 0,43, which suggests a moderate correlation in both cases. Therefore, considering the fact that data begins immediately after fortification with folate was implemented, all neural tube defects decreased in frequency. The graph bellow shows that, after the recommendation of folic acid in pregnancies in 1991, the number of NTD decreased, reaching a minimum in 1998 for anencephaly and encephalocele, and in 1999 for spina bifida.

Figure no. 3. The relationship between neural tube defects. The orange line represents spina bifida, the grey line encephalocele, the blue line anencephaly

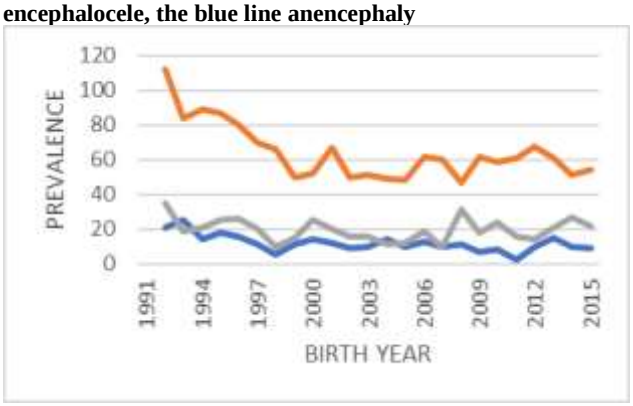


Table no. 1. Gender ratios in neural tube defects

NTD	females	males	gender ratio female/male
anencephaly	157	128	1.226563
spina bifida	760	779	0.97561
encephalocele	229	244	0.938525

Based on data, anencephaly's gender ratio is inclined towards females, while other defects sex ratio is balanced, if not inclined towards males. The explanation for this is, probably, folic acid fortification. As a study conducted over the sex ratios of NTD in South America suggested, male embryos are less influenced by the effects of folic acid than females. As a result, the prevalence of males affected by NTD remained relatively constant, while female prevalence decreased.(7)

DISCUSSIONS

This study used a large amount of data covering a big time period. However, data was not categorized taking into account minorities. As a result, the interpretation includes all ethnic groups.

The data shows a decrease in the number of female patients with anencephaly in comparison with male patients. While the male patient count remained relatively constant, the female patient count saw a decrease in incidence. However, studies show that there is a sex-ratio variation of incidence within different populations.

The decreasing tendencies show that folic acid supplements are effective in anencephaly and spina bifida prevention. However, encephalocele's case count did not respond effectively to folate supplements according to data.

NTD are multifactorial, as a result there are also environmental factors involved. Some risk factors can include maternal folic acid deficiency, obesity, diabetes, teratogens factors (lead, arsenic, pesticides, influenza virus). Low social status has also been associated with a higher rate of NTD.

According to a study conducted in 2015 regarding the anencephaly and spina bifida prevalence in Europe during 1991-2011, voluntary folic acid fortification has proven ineffective in preventing NTD. As a result, in Europe, the prevalence of NTD in 2011 is similar to that in 1991 and no downwards trend was observed in the study.(8)

Studies involving mice indicated that female embryos are at a higher risk of developing NTD than males. One hypothesis suggests the increased number of females with NTD is related to the presence of two X chromosomes in the genome. Abnormal methylation of the X chromosome has been associated with NTDs, suggesting an epigenetic cause. Environmental factors are also important, as female embryos are more sensitive to teratogens factors.(9,10)

CONCLUSIONS

Because of the mandatory folic acid fortification before pregnancy, anencephaly cases decreased from 1992 to 2015. Folate is the only current method in preventing NTD. However, the incidence will still persist because the multifactorial trait of these diseases. Despite folic acid fortification is mandatory in the United States, European countries are hesitant to introduce mandatory fortification.

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